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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification 6 : A61K 38/00 | A2 | (11) International Publication Number: WO 99/13894 (43) International Publication Date: 25 March 1999 (25.03.99) |
| <p>(21) International Application Number: PCT/EP98/05797</p> <p>(22) International Filing Date: 11 September 1998 (11.09.98)</p> <p>(30) Priority Data: 97116220.1 18 September 1997 (18.09.97) EP</p> <p>(71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Gren- zacherstrasse 124, CH-4070 Basle (CH).</p> <p>(72) Inventor: ZAHM, Friederike; Stattstrasse 18, D-79104 Freiburg (DE).</p> <p>(74) Agent: MEZGER, Wolfgang; Grenzacherstrasse 124, CH-4070 Basle (CH).</p> | | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p> |
| <p>(54) Title: USE OF IFN-α AND AMANTADINE FOR THE TREATMENT OF CHRONIC HEPATITIS C</p> <p>(57) Abstract</p> <p>The present invention provides the use of IFN-α in association with Amantadine for the manufacture of medicaments for the treatment of chronic hepatitis C infections. The present invention also provides medicaments containing the IFN-α and Amantadine as a combined preparation for simultaneous, separate or sequential use in therapy of chronic hepatitis C infections. The present invention further provides a method for treating chronic hepatitis C infections in patients in need of such treating comprising administering an amount of IFN-α in association with an amount of Amantadine effective to treat hepatitis C.</p> | | |

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Use of IFN-alpha and Amantadine for the treatment of chronic
hepatitis C

The present invention relates to the field of treatment of chronic hepatitis C infections using an amount of IFN- α in association with Amantadine effective to treat hepatitis C.

Interferons (IFNs) are naturally occurring proteins which have antiviral, antiproliferative and immunoregulatory activity. Four distinct classes of interferons are known to exist in humans (Pestka et al. (1987) Ann. Rev. Biochem. 56, 727-777 and Emanuel & Pestka (1993) J. Biol. Chem. 268, 12565-12569). The IFN- α family represents the predominant class of IFNs produced by stimulated peripheral blood leukocytes (Pestka et al., loc. cit.; Havell et al. (1975) Proc. Natl. Acad. Sci. USA 72, 2185-2187; Cavalieri et al. (1977) Proc. Natl. Acad. Sci. USA 74, 3287-3291), and lymphoblastoid and myeloblastoid cell lines (Familletti et al. (1981) Antimicrob. Agents. Chemother. 20, 5-9). The antiviral effect of IFN- α is achieved not by a direct influence on the viruses themselves, but by an activity on their target cells in the sense of a protection against the virus infection. The interferons can exert effects on cancer tumors and can influence the immune system of the body on that, for example, they activate macrophages and NK cells and intensify the expression of various immunologically significant constituents of the cell membrane. Details of the preparation of interferon-cDNA and the direct expression thereof, especially in *E. coli*, have been the subject of many publications. Thus, for example, the preparation of recombinant interferons is known, for example, from Nature 295 (1982), 503-508, Nature 284 (1980), 326-320, Nature 290 (1981), 20-26, Nucleic Acids Res. 8 (1980), 4057-4074, as well as from European Patents Nos. 32134, 43980 and 211148.

IFN- α monotherapy is commonly used in the treatment of chronic hepatitis C infections, however this treatment is not always effective.

Amantadine has been proposed as monotherapy treatment for chronic hepatitis C infection (JP Smith et al., Treatment of chronic hepatitis C with amantadinehydrochloride, Abstract of the Annual Meeting of the American Gastroenterology Association, May 1996).
5 However, this monotherapy treatment also does not result in response of all patients.

The combination therapy may thus be more effective than either monotherapy.

10 The present invention provides therefore the use of IFN- α in association with Amantadine for the manufacture of medicaments for the treatment of chronic hepatitis C infections. The present invention also provides medicaments containing IFN- α and Amantadine as a combined preparation for simultaneous, separate or sequential use in therapy of chronic hepatitis C infections. In addition, the present
15 invention provides a method for treating chronic hepatitis C infections in patients in need of such treating comprising administering an amount of IFN- α in association with an amount of Amantadine effective to treat chronic hepatitis C.

The term "IFN- α " as used herein includes IFN- α s derived from any
20 natural material (e.g., leukocytes, fibroblasts, lymphocytes) or material derived therefrom (e.g. cell lines), or those prepared with recombinant DNA technology. Details of the cloning of IFN- α and the direct expression thereof, especially in *E. coli*, have been the subject of many publications. The preparation of recombinant IFN- α s is known, for
25 example from Goeddel et al. (1980) *Nature* 284, 316-320 and (1981), *Nature* 290, 20-26, and European Patents Nos. 32134, 43980 and 211148. There are many types of IFN- α such as IFN- α I, IFN- α 2; and further their subtypes including but not limited to IFN- α 2A, IFN- α 2B, IFN- α 2C and IFN- α II (also designated IFN- α II or ω -IFN). The term
30 "IFN- α " also includes consensus IFN- α available from Amgen or mixtures of natural and/or recombinant IFN- α s. The use of IFN- α 2A is preferred. The manufacture of IFN- α 2A is described in European Patents Nos. 43980 and 211148.

The IFN- α used in this invention may be conjugated to a polymer
35 such as a polyalkylene glycol (substituted or unsubstituted), for example

polyethylene glycol, to form PEG IFN- α . Conjugation may be accomplished by means of various linkers known in the art, in particularly by linkers such as those disclosed in European Patent Applications, Publication Nos. 0510356 and 593868 and European
5 Patent Application No. 97108261.5. The molecular weight of the polymer, which is preferably polyethylene glycol, may range from 300 to 30.000 daltons, and one or more, preferably one to three, polymers may be conjugated to the IFN- α . A preferred IFN- α conjugate is formed using IFN- α 2A.

10 Amantadine, tricyclo[3.3.1.1^{3,7}]decane-1-amine, is described in the Merck Index, compound No. 373, Tenth Edition. Its manufacture is described in U.S. Patent No. 3.152.180.

To practice the invention, IFN- α and Amantadine are administered to the patient suffering from chronic hepatitis C infection
15 in amounts sufficient to eliminate or at least alleviate one or more of the signs or symptoms of chronic hepatitis C including elevated ALT, positive test for anti-HCV antibodies, presence of HCV as demonstrated by a positive test for HCV-RNA, clinical stigmata of chronic liver disease and hepatocellular damage.

20 The dosage of IFN- α for practicing the combination therapy of this invention is about 1 to 6 million international units (IU) administered twice or thrice weekly, every other day, or daily. The preferred dosage for practicing the combination therapy of this invention is about 3 million IU administered thrice weekly.

25 The dosage of Amantadine for practicing this invention is about 100 to 400 mg per day, preferably 200 mg. This daily dosage may be administered once per day in a single dose or in divided doses twice or thrice per day.

30 The Amantadine is administered to the patient in association with IFN- α , that is, the IFN- α dose is administered during the same or different periods of time that the patient receives doses of Amantadine. At present IFN- α formulations are not effective when administered orally, so the preferred method of administering the IFN- α is parenterally, preferably by subcutaneous (sc) or intramuscular (im)

injection. The Amantadine may be administered orally in capsule or tablet form in association with the parenteral administration of IFN- α . Of course other types of administration of both medicaments, as they become available are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The effectiveness of treatment may be determined by controlled clinical trials of the combination therapy versus monotherapy. The efficacy of the combination therapy in alleviating the signs and symptoms of chronic hepatitis C infection and the frequency and severity of the side effects will be compared with previous IFN- α and Amantadine monotherapy. Three populations suffering from chronic hepatitis C infection will be evaluated:

1. Patients previously untreated.
2. Patients previously treated with IFN- α or any other drug and who had subsequently relapsed.
3. Patients who were non-responsive to previous treatment with IFN- α or any other drug.

The effectiveness of the combination therapy will be determined by the extent to which the previously described signs and symptoms of chronic hepatitis are alleviated.

Example

Antiviral Effect of Amantadine and IFN- α 2A Against Hepatitis C Virus on Peripheral Blood Mononuclear Cells (PBMC) from Chronic Hepatitis C Patients.

Mononuclear cells from patients with chronic hepatitis C (serum anti-HCV and HCV RNA positive with histologically proven chronic hepatitis) were analysed for the presence of HCV RNA, using reverse transcription and PCR techniques with universal primers from the highly conserved 5' non-coding region of the HCV genome (Navas et al., J. Hepatol. 21, 182-186 (1994)). Typing and subtyping of HCV genomes

were performed by RFLP analysis of PCR products (Navas et al., J. Clin. Microbiol. 21, 317-321(1997)). For the purpose of this study, only cases infected by a single genotype have been considered, in order to minimise the possible interference of multiple genotypes, in the subject population, HCV subtype 1b was prevalent (Pernas et al., J. Gen. Virol. 76, 415-420(1995)). Thus, HCV RNA-positive PBMC obtained from 15 patients have been analysed in vitro for the effects of treatment. PBMC from 10 matched healthy donors have been used as controls and analysed similarly.

PBMC were isolated from heparinized venous blood by Ficoll-Hypaque gradient sedimentation. The interphase PBMC were isolated, washed twice with phosphate-buffered saline, and suspended in RPMI. The viability of these cells was assessed by trypan blue exclusion. PBMC were cultured in duplicate at a concentration of 2×10^6 viable cells/ml in 6-well tissue culture clusters, in a humid atmosphere with 5% CO₂ for 7 days. The cultures have been maintained without mitogens (medium alone) or were stimulated with single mitogens (Phytohemagglutinin (PHA) or Lipopolysaccharide (LPS) or with PHA plus LPS (10 µg/ml each)(Martin et al., Cytokine 8, 313-317 (1996)). PBMC proliferation, and the possible drug-induced cytotoxicity, were measured using non-isotopic cell-proliferation and cytotoxicity assays.

The effect of experimental treatments with Amantadine alone, in combination with IFN- α 2A and those of IFN- α 2A alone, have been established by testing HCV RNA in cultured mononuclear cells, compared with untreated PBMC from patients (Martin et al., supra); specificity controls were as described previously by Navas et al. in J. Hepatol. 21, 182-186 (1994). Treatment of mononuclear cells from healthy donors with Amantadine alone, in combination with IFN- α 2A or with IFN- α 2A alone, served as controls. Changes in HCV RNA concentrations were measured by the AMPLICOR™ HCV MONITOR assay (Roche Diagnostic System, Inc., Branchburg).

Amantadine doses in the physiological range of 1-5µM (2µM corresponds to the therapeutically recommended blood level; daily dose of the drug: 100mg/12 hours) did not affect the cell viability and had minor effects on the response to mitogens during cultures PBMC isolated from HCV patients and healthy donors. Higher doses of

Amantadine (50 and 500 μ M) were only investigated in PBMC from healthy donors. The dose of 50 μ M slightly decreased PBMC proliferation, whereas the dose of 500 μ M showed a marked anti-proliferative effect.

5 All PBMC cultures from HCV patients, but none from donors, were HCV RNA-positive with or without mitogens, as measured by a modification of the AMPLICOR™ HCV MONITOR assay. The dose of 2 μ M Amantadine reduced the mean amount of HCV RNA (number of copies/ μ g RNA) by > 70% either alone and in combination with
10 1000IU/ml IFN- α 2A. In the individual patient, different degrees of reduction in HCV RNA concentration in PBMC were obtained after treatment with 1, 2 and 5 μ M Amantadine alone and in combination with 1000IU/ml IFN- α 2A (Table 1). In addition, HCV RNA became negative in up to 3/15 (20%) PBMC cultures (Table 1).

15 TABLE 1. Number of cases with reduction or disappearance of HCV RNA in PBMC after experimental treatments (n=15)

| | Amantadine (μ M) | IFN- α 2A (IU/ml) | Reduction in HCV RNA concentration | | | |
|----|---------------------------|-----------------------------|---------------------------------------|------|------|----------|
| | | | >25% | >50% | >75% | Negative |
| 20 | 1 | 0 | 3 | 2 | 3 | 0 |
| | 2 | 0 | 5 | 2 | 4 | 1 |
| | 5 | 0 | 2 | 2 | 3 | 3 |
| | 0 | 1000 | 0 | 2 | 3 | 2 |
| 25 | 1 | 1000 | 3 | 3 | 4 | 0 |
| | 2 | 1000 | 3 | 1 | 3 | 3 |
| | 5 | 1000 | 0 | 0 | 2 | 3 |

30 HCV RNA became negative in PBMC cultures from 1/15 (7%) and 3/15 (20%) patients with the doses of 2 and 5 μ M Amantadine, respectively, compared with 2/15 (13%) with IFN- α 2A alone. With the combination of Amantadine and IFN- α 2A 3/15 (20%) PBMC cultures

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resulted HCV RNA negative. The 2 μ M Amantadine / IFN- α 2A combination had better results in the disappearance of HCV RNA in individual PBMC (up to 20% of cases; Table 1) showing a greater effect than the same doses of Amantadine alone.

Claims

1. The use of IFN- α in association with Amantadine for the manufacture of medicaments for the treatment of chronic hepatitis C infections.
- 5 2. Use according to claim 1 wherein the amount of IFN- α is about 1 to 6 million IU twice or thrice weekly, every other day or daily.
3. Use according to claim 1 wherein the amount of Amantadine is 100 to 400 mg daily, preferably 200 mg daily.
4. Use according to claims 1 to 3 wherein the IFN- α is IFN- α 2A or
10 PEG- IFN- α 2A.
5. Medicaments containing IFN- α and Amantadine as a combined preparation for simultaneous, separate or sequential use in therapy of chronic hepatitis C infections.
6. Medicaments of claim 5 wherein the IFN- α is IFN- α 2A.
- 15 7. Medicaments of claim 5 wherein the IFN- α is PEG-IFN- α .
8. Medicaments of claim 5 wherein the IFN- α is PEG-IFN- α 2A.
9. A method for treating chronic hepatitis C infections comprising administering an amount of IFN- α in association with an amount of Amantadine effective to treat chronic hepatitis C.
- 20 10. The method according to claim 9 wherein the amount of IFN- α administered in said method is about 1 to 6 million IU twice or thrice weekly.
11. The method according to claim 9 wherein the amount of Amantadine administered in said method is 100 to 400 mg daily.
- 25 12. The method of any of claims 9 to 11 wherein the IFN- α is IFN- α 2A or PEG-IFN- α 2A.
13. Use of IFN- α and Amantadine for the treatment of chronic hepatitis C infections.

14. The invention as hereinbefore described.

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| (51) International Patent Classification ⁶ : A61K 38/21 // (A61K 38/21, 31:13) | A3 | (11) International Publication Number: WO 99/13894 (43) International Publication Date: 25 March 1999 (25.03.99) |
| (21) International Application Number: PCT/EP98/05797 (22) International Filing Date: 11 September 1998 (11.09.98) (30) Priority Data: 97116220.1 18 September 1997 (18.09.97) EP (71) Applicant: F. HOFFMANN-LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH-4070 Basle (CH). (72) Inventor: ZAHM, Friederike; Stattstrasse 18, D-79104 Freiburg (DE). (74) Agent: MEZGER, Wolfgang; Grenzacherstrasse 124, CH-4070 Basle (CH). | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 3 June 1999 (03.06.99) | |
| (54) Title: USE OF IFN-ALPHA AND AMANTADINE FOR THE TREATMENT OF CHRONIC HEPATITIS C (57) Abstract The present invention provides the use of IFN- α in association with Amantadine for the manufacture of medicaments for the treatment of chronic hepatitis C infections. The present invention also provides medicaments containing the IFN- α and Amantadine as a combined preparation for simultaneous, separate or sequential use in therapy of chronic hepatitis C infections. The present invention further provides a method for treating chronic hepatitis C infections in patients in need of such treating comprising administering an amount of IFN- α in association with an amount of Amantadine effective to treat hepatitis C. | | |

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INTERNATIONAL SEARCH REPORT

In national Application No.

PCT/EP 98/05797

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/21 //(A61K38/21,31:13)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | PALMER SMITH J: "TREATMENT OF CHRONIC HEPATITIS C WITH AMANTADINE" DIGESTIVE DISEASES AND SCIENCES, vol. 42, no. 8, August 1997, pages 1681-1687, XP002057488 see the whole document --- | 1-14 |
| A | SMITH J P: "TREATMENT OF CHRONIC HEPATITIS C WITH AMANTADINE-HYDROCHLORIDE" GASTROENTEROLOGY, vol. 110, no. 4 SUPPL., 19 - 22 May 1996, page A1330 XP002057489 cited in the application see the abstract --- | 1-14 |
| P,A | WO 98 19670 A (T. NAJARIAN) 14 May 1998 see claims --- -/-- | 1-14 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 February 1999

Date of mailing of the international search report

29/03/1999

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Ryckebosch, A

INTERNATIONAL SEARCH REPORT

In ternational Application No

PCT/EP 98/05797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| P,X | J.A. FINDOR ET AL.: "AMANTADINE HCL ALONE AND ASSOCIATED WITH RECOMBINANT ALPHA IFN 2a DURING A SHORT TERM THERAPY IN CHRONIC HCV INFECTION." HEPATOLOGY, vol. 26, no. 4 PART 2, October 1997, page 217A XP002093941 BALTIMORE, MD, US see abstract nr. 354 --- | 1-14 |
| E | WO 98 43625 A (THE PENN STATE RESEARCH FOUNDATION) 8 October 1998 see page 7, line 16 - line 20 ----- | 1,5,9, 13,14 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 98/05797

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 9-13
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 98/05797

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 9843625 A | 08-10-1998 | US 5849800 A | 15-12-1998 |
| | | AU 7099198 A | 22-10-1998 |